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REVIEW ARTICLE

Epstein-Barr virus – associated adenocarcinoma of the stomach: a rare entity with distinct characteristics

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Summary

Undifferentiated gastric carcinoma with intense lymphoid stroma has a close resemblance to nasopharyngeal lymphoepithelioma and is classified as "lymphoepithelioma-like carcinoma" (LELC).

Carcinomas with morphologic features that are identical to those of nasopharyngeal lymphoepithelioma are seen in organs derived from the foregut and are designated as LELC. Most common anatomic sites are the stomach, salivary glands, lung and thymus.

Key words: carcinoma, lymphoepithelioma, stomach

Introduction

Lymphoepithelioma, originally described in nasopharyngeal carcinoma, is histologically characterized by anaplastic tumor cells surrounded by heavy lymphoid cell infiltration [1]. LELC of the stomach constitutes a small subset of gastric cancer with distinct clinicopathological features including involvement of certain parts of the stomach, a better prognosis and a high prevalence of Epstein-Barr virus (EBV) infection [2].

Review of the literature

LELC of the stomach is quite rare and comprises only 1-4% of all gastric carcinomas [2,3]. It has several clinicopathological differences from the common gastric adenocarcinoma. It is preferentially located in the upper and middle parts of the stomach [4-6], has a slightly better prognosis [1], and a strong correlation with EBV infection. Most series report increased incidence of LELC in males.

Endoscopically, LELC of the stomach displays no differences from the common gastric adenocarcinoma whatsoever. In the series of Wang et al. [1], 2 lesions manifested as early gastric cancer of Borrmann type III and 3 lesions manifested as advanced gastric cancer of Borrmann type II/III; only one lesion presented as advanced gastric cancer of Borrmann type I.

Better survival in patients with LELC of the stomach has been reported in several series [1,7,8]. Dense lymphoid infiltration is regarded as a good host defense against tumor cells [4]. Moreover, cases with non-desmoplastic stroma and EBV-related tumor cells are related with better chemotherapeutic results [1,8]. These two factors may contribute to the better survival of patients with LELC of the stomach.

Watanabe et al. [2] initially described the presence of EBV infection in this particular gastric cancer type with lymphoid stroma.

EBV or herpesvirus 4 shows tropism for epithelial and lymphoid cells. It is the causative agent of infectious mononucleosis and is closely related to

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Burkitt's lymphoma, nasopharyngeal carcinoma, and opportunistic B-cell lymphoma in immunocompromised hosts such as patients with acquired immunodeficiency syndrome (AIDS) or the recipients of organ transplants [8]

The association of EBV with gastric carcinomas has been well established over several years. With respect to the worldwide frequency of EBV-associated gastric carcinoma the percentage of positive cases among all non-selected histological types varies from one country to another [9]. Herrera et al. reported a 8.15% prevalence of EBV infection in gastric carcinomas [9], Selves et al. 8.5% [10], Galetsky et al. 8.7% [11], Tokunaga et al. 6.9% [4], and Ott et al. 18% [12]. Variations in those percentages may be due to the relative proportions of the different histological types among EBV-positive carcinomas in the various case series. For example, Galetsky et al. [11] do not include LELC, while Ott et al. [12] include them; if they are excluded their percentages go from 18% to 8.8%.

The prevalence of EBV positivity among LELC of the stomach is one of the highest reported. In the series of Herrera et al. in Mexico [9] it is 45.5%, while Tokunaga et al. [4] report an incidence of 84.6% LELC of the stomach positive for EBV infection.

Although it is widely accepted that EBV is in some degree responsible for that kind of gastric carcinoma, the subtle mechanism of malignant transformation remains unclear [9]. In most studies, EBV only existed in tumor cell and dysplastic epithelium rather than in lymphoid stroma and gastric epithelia [4,5,13,14]. Based on the monoclonality of the EBV DNA and the uniform distribution of the EBV in all malignant cells, it was suggested that EBV infection occurs in the early stages of carcinogenesis [2,15]. However, the virus genome was detected only in dysplasia and carcinoma cells but not in normal epithelium, suggesting that EBV infection may occur during the evolution of dysplasia [16]. Most probably some benign changes in the gastric mucosa associated with an increased risk for gastric cancer, such as chronic gastric atrophy or intestinal metaplasia, may induce the expression of an EBV receptor and therefore allow infection to precede transformation [1].

The exact mechanism of the infection route also remains unknown. It is assumed that the infection of the gastric epithelium occurs through contiguous spread from the nasopharynx, and that explains the preferential localization of LELC in the proximal parts of the stomach [17].

The role of the *H. Pylori* infection in the pathogenesis of LELC has not been well documented. In a study by Lin et al. [18] the prevalence of *H. Pylori* infection was found similar in both LELC and common gastric adenocarcinoma, but was higher than in the normal population. On the other hand, Levine et al. reported a significantly greater reactivity to *H. Pylori* in EBV- negative gastric cancer cases than in controls, but there was no significant difference between EBV-positive cases and controls [19]. More cases are required to elucidate the interactive role of EBV and *H. Pylori* infection in the multistep gastric tumorigenesis.

We recently dealt with a case of a 72-year-old woman with anorexia, mild epigastric pain and weight loss. A gastric tumor close to the pylorus measuring 3.5×3.2 cm was demonstrated radiologically and endoscopically. Gastric cancer was diagnosed by endoscopical biopsy and the patient underwent total gastrectomy. Histologically, the resected tumor showed poorly differentiated gastric carcinoma with prominent lymphoid stroma (Figure 1), and was diagnosed as LELC of the stomach. EBV in the tumor was positive by polymerase chain reaction and *in situ* hybridization.

Conclusion

LELC is an uncommon type of gastric carcinoma, strongly related with EBV presence. This infection is most probably responsible for LELC's distinct clinicopathological features, differentiating it from the common gastric adenocarcinoma.

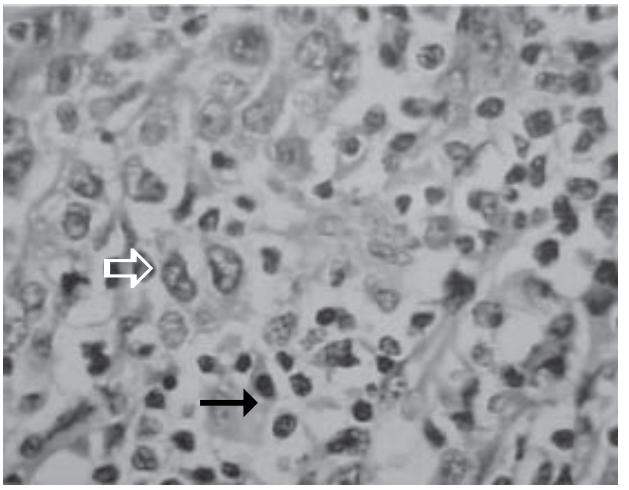

Figure 1. Lympoepithelioma-like carcinoma of the stomach. Anaplastic tumor cells(white arrow) and lympoid cell (black arrow) infiltration (H&E ×300).

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